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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,032	02/05/2004	Frank D. Lee	EPT-001C2	5991

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GOODWIN PROCTER LLP
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EXAMINER

LIN, JERRY

ART UNIT	PAPER NUMBER
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1631

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,032	LEE ET AL.	
	Examiner	Art Unit	
	Jerry Lin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 13, 19-21, 23, 24, 26-28, 30-34, 42 and 44-47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 13, 19-21, 23, 24, 26-28, 30-34, 42 and 44-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3 pages (10/27/2006)</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 18, 2006 has been entered.

Status of the Claims

Claims 1-9, 13, 19-21, 23, 24, 26-28, 30-34, 42, and 44-47 are under examination.

Claims 10-12, 14-18, 22, 25, 29, 35-41, 43 are cancelled.

Information Disclosure Statement

2. The International Search Reports listed as C32, C33 and C34 have not been considered, because the search reports are not publications.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-9, 13, 19-21, 23, 24, 26-28 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claim 1 was amended in step (1) to include the phrase "a least one" It is unclear to what this phrase refers. The phrase may refer to PETs, binding surfaces, target proteins, etc. For purposes of this examination, the Examiner will interpret this phrase to refer to PETs.

Instant claim 9 was amended to include an "amino acid sequence" comprising a splice junction. However, it is understood in the art that splices and splice junctions occur in RNA, not in amino acid sequences. Thus it is unclear what is meant by a splice junction found in an amino acid sequence.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katz (US 2002/0137119 A1) in view of Kohlberger et al. (Gynecologic Oncology (1997) Volume 66, pages 227-232).

The instant methods are drawn to a method of detecting and quantifying target proteins in a sample by fragmenting proteins in a sample, exposing the fragmented proteins to an addressable array of capture agents.

In addition, the examiner is interpreting peptide epitope tags as epitopes that are found on peptides, since there is no explicit definition of the term in the specification.

It is noted that although the instant claims recites that proteins from splice variants of a DNA are present in the biological sample, the steps of the instant claim does not include any detecting or quantifying of these proteins.

Regarding claims 30 and 34, Katz teaches a method of fragmenting proteins using a predetermined denaturation and proteolytic protocol to generate a solution of polypeptide analytes comprising peptide epitope tags that indicate the presence of the sample of the protein (page 8, paragraphs 0136-0147); providing an addressable array of capture agents that can interact with the peptide epitope tag (page 8, paragraphs 0139-0140); contacting the array to the solution (page 8, paragraph 0141).

However, Katz does not teach using detecting and quantifying a plural target splice variant proteins, which are the expression products of one or more splice variants of a single DNA.

Kohlberger et al. teach creating capture agents specific for splice variants (page 230, left column, top).

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the methods of Katz and Kohlberger et al. to gain the benefit of determining the severity of malignant tumors. Katz states that his teachings are used to detect the presence and severity of a disease (abstract). Thus he proposes the use of an array that may be fitted with antibodies that are specific to the peptides of interest (page 8, paragraphs 0139-0140). In one scenario, Katz teaches the using tumor samples and detecting proteins specific to tumors (page 4, paragraph 0062) to detect the severity of a disease. Kohlberger et al. teach the presence and quantities of CD44 splice variants in tumors have been associated with metastasis and poor prognosis, i.e., the severity of a disease (abstract). Given that Katz teaches using antibodies specific for antigens in tumors and Kohlberger et al. teaches how to create antibodies specific for a particular type of antigen found in tumors, one of ordinary skill in the art seeking to determine the severity of malignant tumors would be motivated to combine the methods of Katz and Kohlberger.

Regarding claim 31, Katz teaches that the solid support may be beads or an array device with features that encode the identify of the capture agents (page 8, paragraph 0140; page 14, paragraph 0191).

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Regarding claim 32, Katz teaches where there are 2-100 capture agents (page 14, paragraph 0191).

Regarding claim 33, Katz teaches using a single chain antibody (page 7, paragraph 0127).

6. Claims 1, 3-5, 7-9, 19, 21, 24, 28, 42, 44, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katz (US 2002/0137119 A1) in view of Kohlberger et al. (Gynecologic Oncology (1997) Volume 66, pages 227-232) further in view of Suzuki et al. (US 5,955,317).

The instant methods are drawn to a method of detecting and quantifying target proteins in a sample by fragmenting proteins in a sample, exposing the fragmented proteins to an addressable array of capture agents, and using a secondary capture agent labeled with a detectable moiety to detect a captured fragment.

In addition, the examiner is interpreting peptide epitope tags as epitopes that are found on peptides, since there is no explicit definition of the term in the specification.

Regarding claims 1, 42, and 44, Katz teaches a method of fragmenting proteins using a predetermined denaturation and proteolytic protocol to generate a solution of polypeptide analytes comprising peptide epitope tags that indicate the presence of the sample of the protein (page 8, paragraphs 0136-0147); providing an addressable array of capture agents that can interact with the peptide epitope tag (page 8, paragraphs 0139-0140); contacting the array to the solution (page 8, paragraph 0141).

Although Katz teaches that a variety of detection methods may be used and detecting a types of peptides, Katz does not specifically teach using a secondary capture agent to detect analytes, nor does Katz explicitly teach detecting alternative splicing form proteins.

Regarding claims 1, 42 and 9, Kohlberger et al. teach creating capture agents specific for splice variants and detect the splice variants (page 230, left column, top).

However, Kohlberger et al. does not teach using a secondary capture agent to detect analytes.

Regarding claims 1, 42 and 5, Suzuki et al. teaches using a sandwich assay where the secondary capture agents are specific for a captured polypeptide and labeled with a detectable moiety (column 3, line 40- column 3, line 20; column 8, lines 3-19).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Katz and Kohlberger et al. with Suzuki et al. to gain the advantage of being able to detect a biomarker for Alzheimer's disease. The motivation to combine Katz and Kohlberger et al. is provided above. Katz teaches a general method of detecting proteins in a sample. Katz states that her method may be used for diagnosing a variety of disease including Alzheimer's disease (page 9, paragraph 0132). Thus one of ordinary skill in the art using Katz's method would seek out antibodies that are highly specific for biomarkers of Alzheimer's disease. Suzuki et al. disclose an antibody that is highly specific for a biomarker of Alzheimer's disease (column 3, lines 1-15). Thus one of ordinary skill in the art, seeking to diagnose Alzheimer's disease among other disease such as tumor progression, would be

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motivated use the antibodies disclosed in Suzuki et al.'s method with the antibodies of Kohlberger et al. in the array of Katz.

Regarding claims 3, 4, and 46, Katz teaches where the capture agents are antibodies or nonantibody polypeptides (page 8, paragraph 0139, 0147).

Regarding claims 7 and 8, Katz teaches creating a biopsy digest (page 14, paragraphs 0187-0189) which would contain multiple forms of protein such as pro-form or mature form proteins.

Regarding claim 19, Katz teaches a variety of sample sources (page 8, paragraph 0136).

Regarding claim 21, Katz teaches treating membrane bound proteins (page 13, paragraph 0178)

Regarding claim 24, Katz teaches where the label may be a fluorophore (page 8, paragraph 0142).

Regarding claim 28, Katz teaches where the target proteins may serve as a biomarker (page 8, paragraph 0132).

7. Claims 1-9, 13, 19-21, 23, 24, 26-28, 44, 45, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katz (US 2002/0137119 A1) in view of Kohlberger et al. (Gynecologic Oncology (1997) Volume 66, pages 227-232) in view of Suzuki et al. (US 5,955,317) in view of Wagner et al. (US 6,897,073 B2).

Katz, and Kohlberger et al., and Suzuki et al. are applied as above.

However, Katz does not teach determining the amount of target protein in the sample by averaging the results obtained from each said capture agent.

Regarding claims 2, 20, 21, and 45, Wagner et al. also teach a method of detecting proteins using arrays of protein-capture agents (abstract) which includes contacting the array with cleaved or denatured protein analytes (membrane bound proteins) from body fluids (column 35, lines 22-44) and quantifying the amount of a target protein by averaging the result (including if the total amount of the detected proteins is averaged by one spot in the array) (column 35, line 63-column 36, line 23; column 39, lines 12-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the methods from Katz, Kohlberger et al., Suzuki et al. and Wagner et al. to gain the advantage of creating arrays that can process multiple proteins. The motivation to combine Katz, Kohlberger et al., and Suzuki et al. is applied as above. Although Katz and Suzuki et al. teach using arrays of antibodies, Wagner et al. has the added benefit of detecting and quantifying multiple proteins. Thus one of ordinary skill in the art seeking to detect and quantify a large number of proteins in a sample, for example several biomarkers of Alzheimer's disease, would be motivated to utilize Wagner et al.'s teachings with Katz and Suzuki et al.

Regarding claims 6 and 47, Wagner et al. teach arrays with capture agents bind to the same PET (column 12, line 14 - column 13, line 30), furthermore, Wagner et al.

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teach finding proteins that bind to the same PET at different affinities (column 30, line 54 – column 34, line 45).

Regarding claims 7 and 8, Wagner et al. teach using cellular extracts which would contain multiple forms of protein such as pro-form or mature form proteins (column 35, lines 22-44).

Regarding claims 13, Wagner et al. teach detecting protein fragments (processed forms) of cellular extracts and determining the ratio of one form of protein to another form (column 45, lines 32-39; column 38, lines 43-65).

Regarding claim 23, Wagner et al. teach wherein a secondary capture agent may be used for detection using fluorescent methods (column 36, lines 24-57).

Regarding claim 26, Katz teaches wherein the sample contains billion molar excess of unrelated proteins or fragments (page 13, paragraphs 0178-0183).

Regarding claim 27, Wagner et al. teach wherein the PET is identified based on a sequenced genome (column 30, lines 42-54).

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerry Lin whose telephone number is (571) 272-2561. The examiner can normally be reached on 10:00am-6:30pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Representatives are available to answer your questions daily from 6 am to midnight (EST). When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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PRIMARY EXAMINER

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